PATENT COOPERATION TREATY

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRIERLEY, Anthony, Paul
Appleyard Lees
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ROYAUME-UNI

Date of mailing (day/month/year)
14 March 2001 (14.03.01)

Applicant's or agent's file reference
APB/MER/Q269

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/01719

International filing date (day/month/year)
16 June 1999 (16.06.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

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3. Further observations, if necessary:

4. A copy of this notification has been sent to:

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[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
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Authorized officer
V. Gross

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

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(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRIERLEY, Anthony, Paul
Appleyard Lees
15 Clare Road
Halifax HX1 2HY
ROYAUME-UNI

Date of mailing (day/month/year)
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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
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Date of mailing (day/month/year) 14 August 2000 (14.08.00)	
International application No. PCT/GB99/01719	**Applicant's or agent's file reference** APB/MER/Q269
International filing date (day/month/year) 16 June 1999 (16.06.99)	**Priority date** (day/month/year) 16 December 1998 (16.12.98)
Applicant PAYNE, Lloyd, James et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

11 July 2000 (11.07.00)

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[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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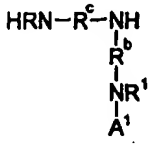

(A)

(57) Abstract

A process for preparing polyamines of, for example, formula (A) includes a step (a) of treating a compound which incorporates a moiety of formula: (I) SS–NR–R^c–NH– with a compound which incorporates a moiety of formula: (II) –NR^1–R^b–L and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group –NR– of moiety (I) to the support, R represents a hydrogen atom or an optionally–substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally–substituted alkyl or aryl group, R^b and R^c each independently represents an optionally–substituted alkylene or alkenylene group and L represents a leaving group and wherein A^1 is a substituent group.

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PROCESS FOR PREPARING POLYAMINES

This invention relates to a process for preparing polyamines and particularly, although not exclusively, relates to a solid phase process and/or a process which can readily be used in a combinatorial or parallel array technique.

Several naturally occurring polyamine amide compounds have shown neurological activity and have glutamate receptor antagonist activity. Hitherto, they have been considered for use in the treatment of neurological disorders such as Alzheimer's disease, Huntingdon's chorea, stroke and brain trauma.

Traditionally, the compounds have been isolated from natural sources such as spider and wasp venom's; however, isolation and purification of the compounds can be problematical.

Attempts have been made to synthesise polyamine amides, for example as discussed in Pharmaceutical Sciences (1997), 3,223-233, Chem Letts (1993) 929-932, Chem Pharm Bull 44(5) 972-979 (1996) and by I.R. March and M. Bradley in Tetrahedron 1997, Vol 53, pages 17317 to 34. In the latter reference, a protected polyamine is prepared in solution and is then attached to a resin and used in a solid phase process. However, the solution preparation is hard, tedious and time-consuming and it is difficult to prepare polyamines in a parallel manner. Consequently, desired amines tend to be made one at a time, using the known art.

It is an object of the present invention to provide an advantageous process for preparation of symmetrical and unsymmetrical polyamines.

According to a first aspect of the invention, there is provided a process for preparing a polyamine compound which includes a step (a) of treating a compound which incorporates a moiety of formula:

$$SS\text{-}NR\text{-}R^{c}\text{-}NH\text{-} \qquad I$$

with a compound which incorporates a moiety of formula:

$$-NR^{1}\text{-}R^{b}\text{-}L \qquad II$$

and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group -NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

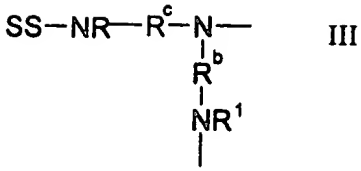
Unless otherwise stated in this specification, where any group is stated to be optionally-substituted, it may be substituted by one or more substituents. Suitably, it may be substituted by up to 4, preferably up to 3, more preferably up to 2, especially up to 1 substituent.

Unless otherwise stated in this specification, where any group is stated to be optionally-substituted, optional substituents may be selected from halogen (preferably fluorine, chlorine or bromine) atoms and optionally substituted, preferably unsubstituted, alkyl, acyl, aryl, nitro, cyano, alkoxy, alkoxyalkyl, hydroxy, amino, alkylamino (including dialkylamino), sulphinyl, alkylsulphinyl, carbamoyl (including alkylcarbamoyl and dialkylcarbamoyl), sulphonyl, alkylsulphonyl, sulphonate, amido, alkylamido, alkoxycarbonyl, halocarbonyl (especially chlorocarbonyl), haloalkoxy, and haloalkyl (especially fluoroalkyl or chloroalkyl), groups.

Unless otherwise stated in this specification, an alkyl, alkenyl, alkylene or alkenylene group may have up to 12, suitably up to 10, preferably up to 8, more preferably up to 6, especially up to 4, carbon atoms.

Unless otherwise stated in this specification, an aryl group is suitably an aromatic or heteroaromatic group which preferably has 6 to 10 ring atoms and, more preferably, has 6 or 10 ring atoms. Examples of aromatic groups include phenyl, 1-naphthyl and 2-naphthyl groups of which the phenyl group is preferred. Heteroaromatic groups may include one or more O, N or S atoms or combinations thereof.

The process suitably produces a compound which incorporates a moiety:



III

which may subsequently be optionally derivatized and/or a compound prepared may be detached from said SS moiety and/or said compound prepared may be optionally derivatized after detachment.

Preferably, R represents a hydrogen atom or an optionally-substituted, preferably an unsubstituted, alkyl group. More preferably, R represent a hydrogen atom.

R^b and R^c may independently have up to 10, suitably up to 8, preferably up to 6, more preferably up to 4, carbon atoms in a straight chain. R^b and R^c may have the same number of carbon atoms in a straight chain in which case compounds which include moiety III (and compounds moieties produced in downstream processes) may be symmetrical polyamines. However, R^b and R^c may have a different number of carbon atoms in a straight chain in which case compounds which include moiety III (and compounds/moieties produced in downstream processes) may be unsymmetrical polyamines. Unsymmetrical polyamines can be quite difficult to prepare by known processes; however, the process described herein can relatively easily be used to make such compounds. Preferably, R^b and R^c independently have 3 or 4 carbon atoms in a straight chain. More preferably, R^c has 4 carbon atoms and R^b has 3 carbon atoms in a straight chain.

R^b and R^c may independently be optionally substituted by 1 or 2 optionally-substituted, preferably unsubstituted, alkyl groups, wherein each alkyl group suitably has 1 to 3 carbon atoms.

R^1 suitably represents a hydrogen atom or a C_{1-10}, preferably C_{1-8}, more preferably C_{1-6}, especially C_{1-4}, alkyl group or an aryl group, said alkyl or aryl group being optionally-substituted, preferably by one or more substituents selected from halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is alkyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof.

Suitably, in said moiety II (and suitably in other moieties which include R^1), R^1 represents a hydrogen atom or an optionally-substituted, preferably an unsubstituted, alkyl or aryl group. Preferably, R^1 represents a hydrogen atom or an optionally-substituted alkyl group.

Said moiety of formula I may be part of a structure of formula:

SS-NR-R^c-NHP^1 IV

wherein P^1 represents a protecting/activating group. P^1 is preferably an electron-withdrawing group. It is preferably adapted to increase the acidity of the hydrogen atom of the group -NHP^1. P^1 preferably forms a sulphonamide group with moiety I. Thus, P^1 preferably represents a moiety:

$-SO_2-X^1$ V

wherein X^1 represents an optionally-substituted aryl, especially phenyl, group. Said optionally-substituted aryl group may include one or more substituents. Preferred substituents are electron-withdrawing groups. A nitro group is a preferred optional substituent. A 4-nitro or a 2,4-nitro is especially preferred. Preferably, X^1 represents a di-nitrophenyl group.

The mechanism of the reaction of moieties I and II is believed to involve attack of the nucleophilic nitrogen atom of moiety -NH- of moiety I with a carbon atom adjacent to leaving group L in moiety II. L is preferably an electron-withdrawing group. Consequently, the leaving group L is displaced.

L may need to be activated to act as a leaving group in the reaction. L may be any leaving group which may be electronegative and/or be capable of functioning in the mechanism referred to. L may be a halogen atom, preferably a bromine or chlorine atom, especially a bromine atom, or a hydroxy group. The ability of the hydroxy group to act as a leaving group may be caused and/or enhanced by other reagents used in the reaction.

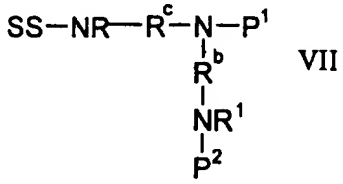
Said moiety of formula II may be part of a structure of formula:

$P^2NR^1-R^b-L$ VI

wherein P^2 represents a protecting group. Preferred protecting groups include N-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl and Triethlsilyloxycarbonyl (TEOC). The former is preferred.

Preferably, SS represents a solid support resin which includes linking means. Said linking means may include a -O-CO- moiety, the carboxy end of which is suitably bonded to the nitrogen atom of the moiety -NR- of moiety I. The alkoxy end of the -O-CO- moiety may be bonded to the resin by suitable means which is preferably an alkylene group, especially a $-CH_2-$ group. Said solid support resin may be any suitable resin, for example a polystyrene resin. Suitably, the linking means is a Wang linker.

In Step (a), swollen resin of formula I (which may suitably be swollen in anhydrous tetrahydrofuran), triphenylphosphine and a said compound which incorporates moiety II (especially compound VI) may be stirred together and, subsequently, a coupling agent, suitably diethylazodicarboxylate, is added, slowly. The mixture may be stirred for about 12 hours, filtered, washed and dried. The product of the reaction suitably incorporates moiety III and is suitably protected by groups P^2 and P^1 and is, therefore, of formula:



VII

Said compound VI may be prepared by a reaction known to a person skilled in the art, wherein P^2 is a protecting group.

Said compound IV may be prepared in a step (-b) which comprises reaction of a compound of general formula:

$$SS\text{-}NR\text{-}R^c\text{-}NH_2 \qquad VIII$$

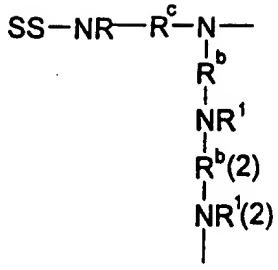
with a compound of formula P^1L^2 wherein L^2 is a leaving group, especially a chlorine atom. The reaction is preferably carried out in the presence of a base, for example 2,6-lutidine and in an organic solvent.

Said compound of formula VIII may be prepared in a step (-c) by reaction of a compound of formula

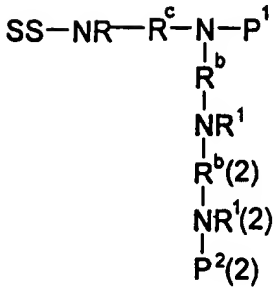
$$HRN\text{-}R^c\text{-}NH_2 \qquad IX$$

with a structure $SS\text{-}L^3$ wherein L^3 represents a leaving group which may include an imidazole moiety.

Compound VII and/or said compound incorporating moiety II can readily be derivatised to produce a wide range of compounds, suitably in a parallel array or combinatorial chemistry technique. In a first embodiment, compound VII and/or said compound incorporating moiety III may be treated with a further compound which incorporates a moiety of formula II (which moiety may include R^1, R^b and L which are the same as or different to such groups used in Step (a)) as described above thereby to prepare a compound which incorporates the moiety



or is of formula



wherein $R^b(2)$, $R^1(2)$ and $P^2(2)$ may be any group described herein for R^b, R^1 and P^2 respectively except that they may be the same or different to groups R^b and R^1 used in Step (a) and P^2 as described above.

In the derivatisation reaction of the first embodiment, said compound of formula VII may be reacted to remove P^1 and replace it with, for example another protecting group (e.g. Boc) and P^2 may be removed and replaced with a protecting/activating group of type P^1 discussed above. The derivatised compound VII prepared

may then be treated, for example with a structure of formula:

$P^2NR^1(2)-R^b(2)-L$

wherein P^2 and L are as described above (although they could be different from P^2 and L used in Step (a)). The reaction may be carried out under conditions as described above for Step (a).

The derivatisation of the first embodiment may be further repeated to add successive groups $-NR^1(3)-R^b(3)-$ etc.

Compound VII (or derivatives thereof prepared as described in said first embodiment) may be derivatized by a range of compounds, for example amino acids, may be coupled to moiety $-NR^1-$ (or $-NR^1$ (2), $-NR^1$ (3) if provided), thereby replacing protecting group P^2 and, in turn, other compounds, for example further amino acids, may be coupled to said compounds initially coupled to moiety $-NR^1-$ (or $-NR^1$ (2), $-NR^1$ (3), if provided) and/or derivatisation reactions effected. Further coupling reactions may also be effected by techniques known to those skilled in the art.

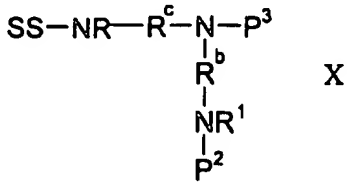
In general terms, a suitably deprotected compound VII and/or said compound incorporating moiety III may be treated with a first reagent (which may be protected) to replace group P^2 in compound VII with a residue of said first reagent. The product (or a derivative), suitably deprotected, may be treated with a second reagent (which may be protected) so that said second reagent becomes

bonded to a said residue of said second reagent. Such treatments may be repeated to react further reagents with the derivative of compound VII.

Suitably, said first reagent is di-functional. Said first reagent preferably includes an aryl group (or a precursor thereof). Said first reagent preferably includes an amine group (or a precursor thereof). Thus, suitably said first reagent (and a or any subsequent reagent) is an amino acid (or a precursor thereof, for example a protected version or derivative thereof).

Suitably, said second reagent is di-functional. Said second reagent preferably includes an aryl group (or a precursor thereof). Said second reagent preferably includes an amine group (or a precursor thereof). Thus, suitably said second reagent is an amino acid (or a precursor thereof, for example a protected version or derivative thereof). Further reagents which may be reacted with said second reagent may have any feature of said second reagent as described above.

More specifically, said compound of formula VII may be reacted in a step (b) to substitute the group P^1 with another group which may be another protecting group P^3 or an electrophilic reagent. Group P^3 may be an acyl, -Boc, alkyl, or sulphonyl group. Thus, the product of step (b) may be a compound of formula

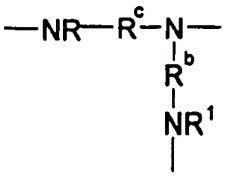


Protecting group P^2 may next be removed from compound (X) in a step (c) so that P^2 is replaced by a hydrogen atom (such a compound being referred to as compound XI). Step (c) may involve reaction in hydrazine and an organic solvent or may involve any suitable deprotection reaction.

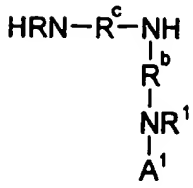
Next, in Step (d), a compound may be coupled to the free $-NH_2$ group of compound XI. For example, an amino acid, suitably an amino acid which is protected by a protecting group orthogonal to the group binding portions of compound X to the solid support of SS, such as an Fmoc protected amino acid (i.e. "Fmoc AA"), may be coupled to said free $-NH_2$ group. Suitably, an amino acid selected from those shown in Summary 1 or Summary 2 hereinafter, especially those in Summary 1, may be coupled to said group. Thereafter, other compounds, for example other amino acids, may be coupled, for example to the aforementioned amino acid, in order to produce more complex compounds using procedures know to those skilled in the art. Suitably, an amino acid selected from those shown in Summary 1 or Summary 2 hereinafter, especially those in Summary 2, may be coupled.

Subsequently, the desired compound prepared may be cleaved from the resin and/or optionally derivatised as may be desired.

Such a compound may incorporate a moiety

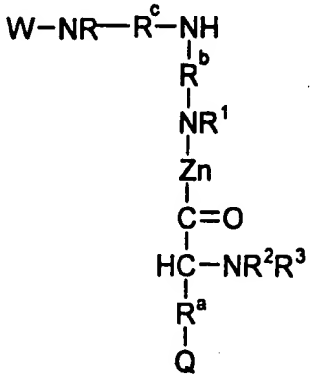


Preferably such a compound is of general formula



wherein A^1 is a substituent group which may comprise one or more optionally derivatised amino acid residues or is a salt of the aforementioned compound.

More preferably, such a compound may be of formula



wherein R, R^c, R^b and R^1 are as described in any statement herein; W is a hydrogen atom or an optionally-substituted, preferably unsubstituted, alkyl or aryl group; Z is an amino acid residue, especially an aromatic amino acid residue; n is zero or a positive integer, preferably in the range 0-10, more preferably 0-4, especially 0 to 1; R^2 and R^3 are the same or different from each other and each represents a hydrogen atom or a

group of formula R^6, R^6CO-, R^6OCO- or R^6NHCO- where R^6 represents an optionally-substituted alkyl group, suitably a C_{1-10}, preferably a C_{1-8}, more preferably a C_{1-6}, especially a C_{1-4}, alkyl group, or an optionally-substituted aryl group, wherein preferred optional substituents of said alkyl and aryl groups are selected from halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is alkyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof; R^a represents an optionally-substituted straight or branched chain alkylene or alkenylene group, preferably an alkylene or alkenylene group having 1 to 6 carbon atoms each optionally-substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms; and Q represents an amidino group, a cyano group or a group of formula XYN-, wherein X and Y are the same or different, and each may represent a hydrogen atom, an alkyl group, (suitably a C_{1-10}, preferably a C_{1-8}, more preferably a C_{1-6}, especially a C_{1-4} alkyl group) or a simple heteroatom-containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group.

The process described according to said first aspect may be used to prepare any of the polyamine compounds described in any of the documents cited in the introduction of this specification; and any of the polyamine compounds described in PCT/GB89/03775 and the polyamine compounds described in each of the aforementioned documents are incorporated herein by reference.

According to a second aspect of the invention, there is provided a process for preparing a plurality of different polyamine compounds which includes a step of:

(a) selecting a plurality of different compounds of general formula I or a plurality of different compounds of formula II or a plurality of different compounds of both formulas I and II and reacting compounds of formula I with compounds of formula II, for example in a combinatorial or parallel array technique, followed by optional derivatisation, thereby to prepare a plurality of different polyamine compounds; OR

(b) derivatising a product of a reaction of a compound of general formula I with a compound of general formula II with a plurality of different compounds, followed by optional derivatisation of the product thereof, thereby to prepare a plurality of different polyamine compounds.

According to a third aspect of the invention, there is provided a library of compounds prepared in a process according to said second aspect.

According to a fourth aspect of the invention, there is provided a product of a process according to said first or second aspect.

According to a fifth aspect of the invention, there is provided any novel intermediate described in any statement herein.

Any feature of any aspect of any invention or embodiment described herein may be combined with any

feature of any aspect of another invention described herein.

Specific embodiments of the invention will now be described, by way of example. In the Examples, the following abbreviations are used:

Arg	arginine;
Boc	t-butoxycarbonyl;
DCM	dichloromethane
Dde	N-1,4(4,4-dimethyl-2,6-dioxocyclohex-1-ylidine) ethyl;
DEAD	diethyl azodicarboxylate;
DIC	di-isopropylcarbodiimide;
DMF	dimethylformamide;
Fmoc	N-fluorenylmethoxycarbonyl;
HOBt	N1-hydroxybenzotriazole;
Lys	lysine;
Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl;
Phe	phenylalanine;
RP-HPLC	reverse phase high performance liquid chromatography;
THF	tetrahydrofuran;
TFA	trifluoracetic acid;
TBTU	2(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEOC	2-(Trimethylsilyl)ethoxycarbonyl.

Example 1 - Preparation of Arginine-L-phenylalanine-spermidine - an unsymmetrical polyamine.

Wang resin (0.03 mmol, 50 mg) was swollen in anhydrous tetrahydrofuran (1.0 ml) and carbonyl diimidazole (4 equivalents, 0.12 mmol, 19 mg) was added. The resulting mixture was then stirred at ambient temperature for 16 hours, after which it was filtered and washed with tetrahydrofuran, ethanol and dichloromethane. The resin was then dried in *vacuo*.

The resin was re-swollen in anhydrous dichloromethane (1.0 ml), and 1,4-diaminobutane (10 equivalents, 0.3 mmol, 25 mg) were added. The resulting mixture was stirred for 2 hours and then filtered and washed (dimethylformamide, methanol, dichloromethane), after which it was dried in *vacuo*.

The resin was again swollen in anhydrous dichloromethane (1.0 ml), and 2,6-lutidine (5 equivalents, 0.15 mmol, 16 mg) were added, followed by the careful addition of 2,4-dinitrobenzenesulfonyl chloride (4 equivalents, 0.12 mmol, 32 mg). The mixture was stirred under an inert atmosphere for 2 hours and then washed (dimethylformamide, methanol, dichloromethane) and dried in *vacuo*.

The resulting resin was then swollen in anhydrous tetrahydrofuran (1.0 ml) and triphenylphosphine (4 equivalents, 0.12 mmol, 32 mg). Dde-protected aminoalcohol (4 equivalents, 0.12 mmol, 29 mg) (prepared as described below) were added and dissolved with stirring. Diethyl azodicarboxylate (4 equivalents, 0.12

mmol, 21 mg) was added dropwise and the mixture was stirred for 12 hours and then filtered and washed (dimethylformamide, methanol, dichloromethane). It was then dried in *vacuo*.

The resin was then swollen in dichloromethane (1.0 ml), and propylamine (5 equivalents, 0.15 mmol, 13 mg) was added. The mixture was then stirred for 1 hour after which it was filtered and washed (dimethylformamide, methanol, dichloromethane) and then dried in *vacuo*.

The resin was again swollen in dichloromethane (1.0 ml), and di-t-butyl dicarbonate (10 equivalents, 0.3 mmol, 33 mg) and N,N-dimethylaminopyridine (5 mol%, 0.0015 mmol, 0.2 mg) were added, and the mixture was stirred for 16 hours. The resin was then filtered and washed (dimethylformamide, methanol, dichloromethane), and then dried in *vacuo*.

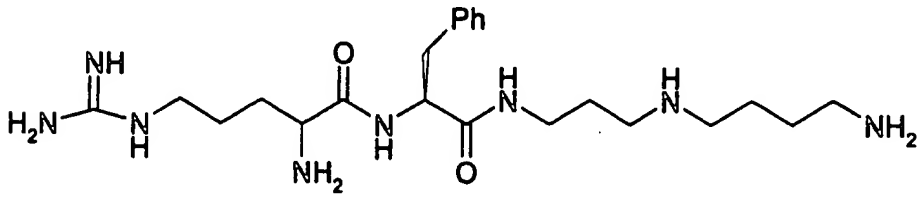
The resin was then stirred in 2% hydrazine hydrate/dimethylformamide (1.0 ml) for 1 hour and then washed (dimethylformamide, methanol, dichloromethane), after which it was dried in *vacuo*.

Fmoc-Phe-OH (4 equivalents, 0.12 mmol, 46 mg), TBTU (4 equivalents, 0.12 mmol, 39 mg) and diisopropylethylamine (8%, 0.48 mmol, 62mg) were dissolved in anhydrous dimethylformamide (1.0 ml), and the mixture was added to the resin. The whole was then stirred for 12 hours, and then filtered and washed (dimethylformamide, methanol, dichloromethane) and dried in *vacuo*.

To the resin was added 20% piperidine/dimethylformamide (1.0 ml) and the mixture was stirred for 0.5 hour. It was then filtered and washed (dimethylformamide, methanol, dichloromethane) and then dried in *vacuo*.

Boc-Arg(Pbf)-OH (4 equivalents, 0.12 mmol, 63 mg), TBTU (4 equivalents, 0.12 mmol, 39 mg), and diisopropylethylamine (8 equivalents, 0.48 mmol, 62 mg) were dissolved in dimethylformamide (1.0 ml) and the mixture was added to the resin. The whole was then stirred for 12 hours and then filtered and washed (dimethylformamide, methanol, dichloromethane). It was then dried in *vacuo*.

50%TFA/45%dichloromethane/2.5%H_2O/2.5% triisopropylsilane (1.0 ml) was added to the resin and the mixture was stirred for 1 hour. The resin was filtered and washed with dichloromethane (1.0 ml) and the filtrate was concentrated in *vacuo*. The resulting viscous yellow oil was triturated with anhydrous diethyl ether (3x2 ml) to yield the title compound as shown below as its tetrakis TFA salt (19 mg, 70%):

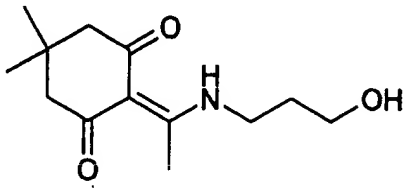


Analysis:

LCMS - 90% (ELS detection). M/z 449 (ES^+).

NMR:- ^1H NMR was found to be in accordance with the above structure

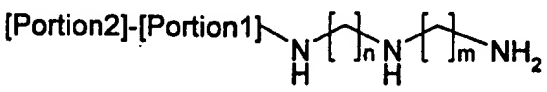
In the above described process, the following Dde protected aminoalcohol was used:



The Dde protected aminoalcohol was prepared as follows: To a solution of 3-amino-1-propanol (1.5 g, 20 mmol) in ethanol was added 2-acetyl dimedone (1.1 equivalents, 22 mmol, 4.0 g) and the mixture was heated to 50°C for 1 hour. The resulting solution was concentrated in *vacuo* to yield a red crystalline solid that was triturated with hexane to afford an off-white solid (4.74g, 95%).

Examples 2 - Preparation of other polyamines

Polyamines having the general structure:



E-I

wherein Portions 1 and 2 are amino acid residues as described hereinafter and wherein n represents 3 or 4 and m represents 4 were prepared using the following general method which is summarised in Scheme 1.

Step 1

Wang resin (0.03 mmol) was swollen in anhydrous THF (1.0 ml) and carbonyl diimidazole (4 eq, 0.12 mmol) added portionwise. The resulting mixture was stirred at ambient temperature for 16 hours then filtered and washed with THF, Et_2O and DCM. The resin was then dried in *vacuo* (Step 1).

Step 2

The resin was re-swollen in anhydrous DCM (1.0 ml) and a symmetrical diamine (NH_2-$(CH_2)_m$-NH_2) (10 eq, 0.3 mmol) added portionwise. The resulting mixture was stirred for 2 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 3

The resin was again re-swollen in anhydrous DCM (1.0 ml) and 2,6-lutidine (5 eq, 0.15 mmol) added followed by the careful addition of 2,4-dinitrobenzenesulfonyl chloride (4 eq, 0.12 mmol). The mixture was stirred under an inert atmosphere for 2 hours then washed (DMF, MeOH, DCM) and dried in *vacuo*.

Step 4

The resulting resin was then swollen in anhydrous THF (1.0 mol) and triphenylphosphine (4 eq, 0.12 mmol), Dde-protected aminoalcohol (DdeHN-$(CH_2)_n$-OH) (4 eq, 0.12 mmol) were added and dissolved with stirring.

Diethylazodicarboxylate (4 eq, 0.12 mmol) was added dropwise and the mixture stirred for 12 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 5

The resin was then swollen in DCM (1.0 ml) and n-propylamine (5 eq, 0.15 mmol) added and the mixture stirred for 1 hour then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

The resin was again swollen in DCM (1.0 ml) and di-t-butyldicarbonate (10 eq, 0.3 mmol) and N,N-dimethylaminopyridine (5 mol%, 0.0015 mmol) added and the mixture stirred for 16 hours. The resin was then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 6

The resin was then stirred in 2% hydrazine hydrate/DMF (1.0 ml) for 1 hour then washed (DMF, MeOH, DCM) and dried in *vacuo*.

Step 7

The Fmoc derivatives of the amino acids shown in Summary 1 (wherein residues thereof are destined to become Portion 1 in the polyamines) were prepared (hereinafter referred to, generally, as "Fmoc AA1"). Then, Fmoc AA1 (4 eq, 0.12 mmol), TBTU (4 eq, 0.12 mmol) and diisopropylethylamine (8 eq, 0.48 mmol) were dissolved in anhydrous DMF (1.0 ml) and the mixture added to the resin.

The whole was then stirred for 12 hours then filtered and washed (DMF, MeOH, DCM) and dried in *vacuo*.

Step 8

To the resin was added 20% piperidine/DMF (1.0 ml) and the mixture stirred for 0.5 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

The Boc derivatives of the amino acids shown in Summary 2 (wherein residues thereof are destined to become Portion 2 in the polyamines) were prepared (hereinafter referred to, generally, as "Boc AA"). Then, Boc AA (4 eq, 0.12 mmol), TBTU (4 eq, 0.12 mmol), and diisopropylethylamine (8 eq, 0.48 mmol) were dissolved in DMF (1.0 ml) and the mixture added to the resin. The whole was then stirred for 12 hours then filtered and washed (DMF, MeOH, DCM) then dried in *vacuo*.

Step 9

50%TFA/45%DCM/2.5%H_2O/2.5% triisopropylsilane (1.0 ml) was added to the resin and the mixture stirred for 1 hour to remove the compound from the resin (Step 9). The resin was filtered and washed with DCM (1.0 ml) and the filtrate concentrated in *vacuo*. The resulting viscous yellow oil was triturated with anhydrous diethylether (3x2 ml) to yield the required compound.

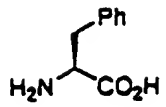
A wide range of compounds were prepared using the general method described and using the amino acids in Summary 1 to provide Portion 1 and the amino acids in Summary 2 to provide Portion 2. It will be appreciated

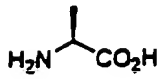
that amino acid residues incorporated into compound E-I comprise the amino acids shown in Summary I and II but excluding hydrogen atoms from the $-NH_2$ and $-CO_2H$ groups.

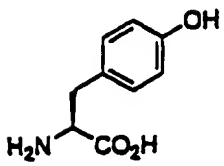
Table 1 summarises a 4,4-polyamine library prepared - that is, a library wherein n and m represent 4; the left column in the table details respective Portion 1's (identified by their letters in Summary 1) used to prepare the compounds; and the top row details respective Portion 2's (identified by their numbers in Summary 2) used to prepare the compounds. Table 2 summarises a 3,4-polyamine library - that is, wherein n represents 3 and m represents 4 with Portions 1 and 2 being identified as before.

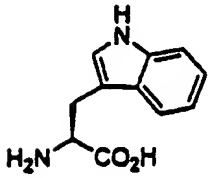
In tables 1 and 2, each box in the table represents a particular compound prepared and the Mass Spec (ES^+) and HPLC Retention Time in minutes are provided in each box (where available).

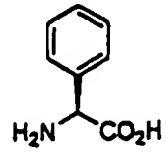
Summary 1 - amino acids used to form "Portion 1" amino acid residues.

A 

B 

C 

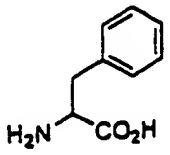
D 

E 

F Portion 1 absent

Summary 2 - amino acids used to form "Portion 2" amino acid residues.

1



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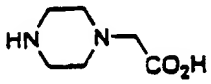

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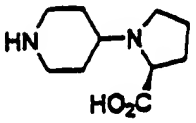

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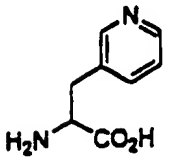

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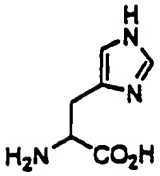

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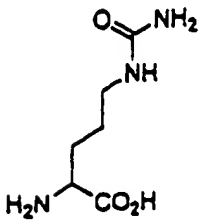

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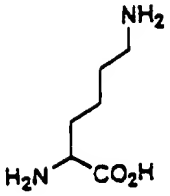

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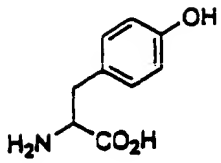

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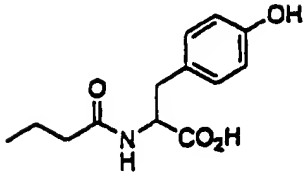

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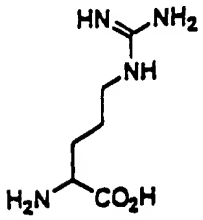

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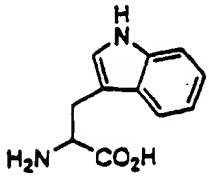

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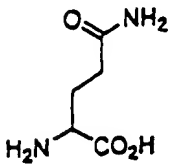
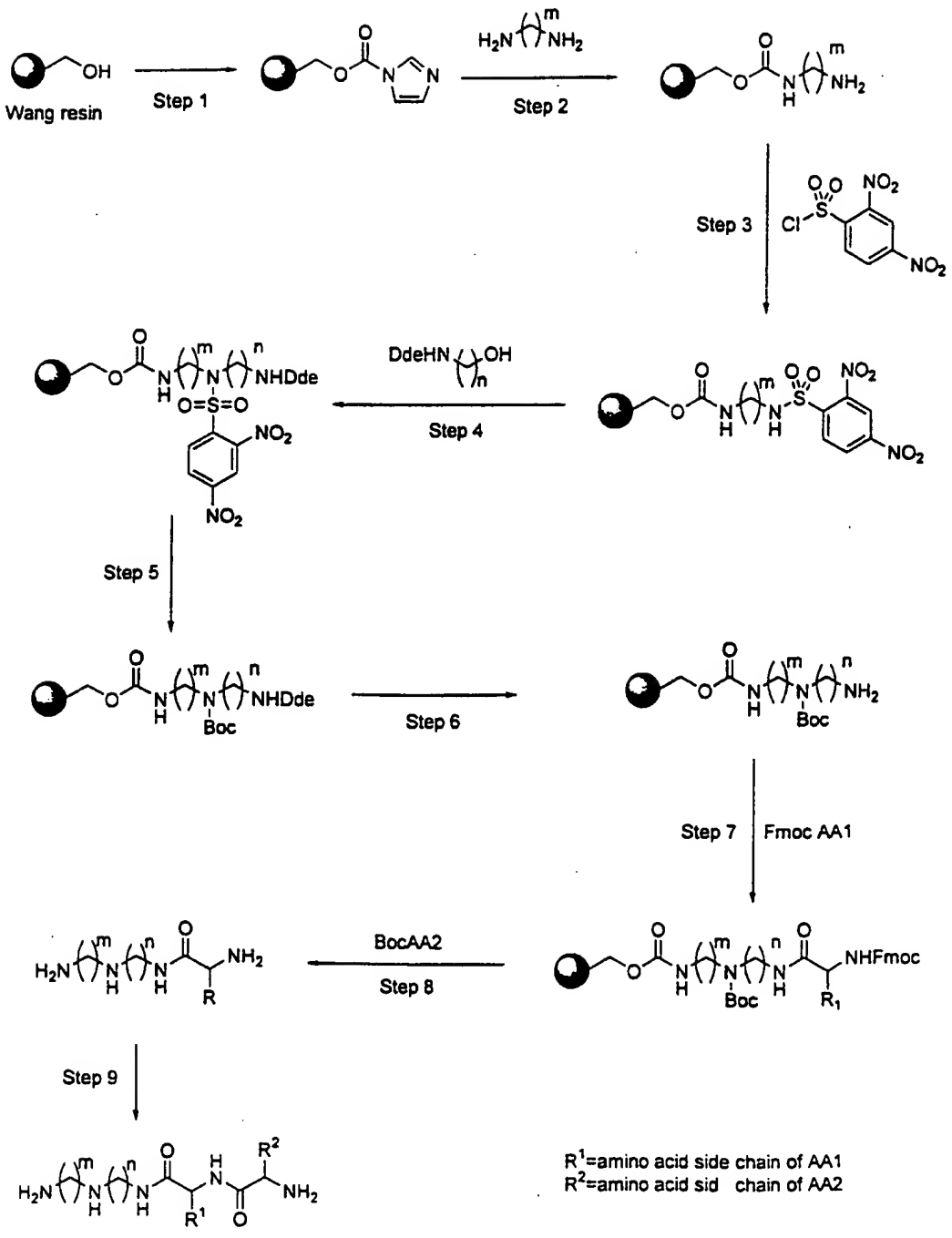


	1	2	3	4	5	6	7	8	9	10	11	12
A	454.17 0.27	433 0.23	487.29 0.24	455 0.24	444 0.26	464 0.26	435 0.25	470 0.26	540 0.49	463 0.25	493 0.29	-
B	378 0.25	357 0.25	411 0.22	379 0.25	368 0.22	388 0.25	359 0.25	394 0.25	464 0.37	387 0.22	417 0.25	-
C	470 0.25	449 0.25	503 0.25	471 0.25	460 0.25	480 0.25	451 0.25	486 0.25	556 0.44	479 0.22	509 0.26	-
D	493 0.26	472 0.25	526 0.23	494 0.25	483 0.22	-	474 0.25	509 0.26	-	502 0.22	-	-
E	-	419 0.24	473 0.25	441 0.25	430 0.24	450 0.24	421 0.26	456 0.26	526 0.48	449 0.23	-	-
F	307 0.25	286 0.25	340 0.25	308 0.25	297 0.23	317 0.25	288 0.22	323 0.23	393 0.35	316 0.23	346 0.25	-

TABLE 1 - 4,4-Polyamine Library.

	1	2	3	4	5	6	7	8	9	10	11	12
A	440.2 0.29	419.2 0.27	473.28 0.26	441.17 0.27	430.2 0.24	450.22 0.27	421.26 0.27	456.21 0.29	526.26 0.5	449.21 0.25	-	-
B	-	343.25 0.26	397.29 0.26	365.24 0.26	354.25 0.26	374.25 0.25	345.25 0.26	380.22 0.26	450.23 0.38	373.3 0.26	403.23 0.26	345.28 0.27
C	456.2 0.27	435.22 0.27	487.28 0.25	457.19 0.21	446.19 0.26	466.24 0.25	437.22 0.27	472.24 0.26	542.24 0.45	465.25 0.27	495.24 0.26	-
D	479.16 0.25	458.18 0.26	412.29 0.26	480.22 0.26	469.26 0.24	489.24 0.26	460.27 0.24	-	565.21 0.5	488.3 0.26	518.2 0.31	460.24 0.26
E	426.21 0.26	405.22 0.26	459.25 0.27	427.18 0.27	416.17 0.26	436.2 0.26	407.24 0.26	442.2 0.28	512.25 0.5	435.22 0.26	-	407.21 0.26
F	293.18 0.26	272.22 0.25	326.25 0.27	294.17 0.26	283.17 0.27	303.2 0.26	274.23 0.25	309.13 0.25	379.22 0.35	302.19 0.26	332.14 0.26	274.19 0.24

TABLE 2 - 3,4-Polyamine Library.


Wang resin
Step 1
Step 2
Step 3
Step 4
Step 5
Step 6
Step 7
Fmoc AA1
Step 8
BocAA2
Step 9
R1=amino acid side chain of AA1
R2=amino acid sid chain of AA2

Example 3 - Alternative reagent for Step 4

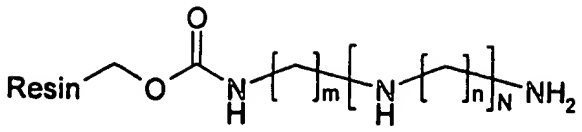
As an alternative to the use of Dde-protected aminoalcohols in Step 4, TEOC may be used.

Example 4 - Derivatives of polyamines

Derivatives of the amines prepared in Examples 1 and 2 may be prepared by reaction with a compound having an electrophilic specie such as an acid chloride, sulphonyl chloride etc. In a specific example, the starting material of Step 5 may be acylated, instead of using di-t-butyldicarbonate to give a Boc protecting group. Acylation may be carried out using a standard technique, using an acid chloride or another activated acid, to produce peptidomimetics. Sulphonyl chlorides may be used to sulphonylate amine groups to produce derivatives.

Example 5

Step 4 in Example 4 may be repeated more than once in order to add further moieties $-NH-(CH_2)_n-$ to the polyamine chain. To this end, after Step 5 in Scheme 1, the Dde group may be removed and the resultant free amine group re-sulphonated in a process analogous to that described in Step 3. The re-sulphonated product may then be treated with a Dde-protected amine alcohol in a process analogous to that described in Step 4. Step 5 may be repeated. Subsequently, further moieties $-NH-(CH_2)_n-$ may be added in the manner described or Step 6 and subsequent steps described may be carried out. Thus, the product of Step 6 may be of formula



wherein N is an integer of 1 or greater and wherein n may be the same or different for each repeat unit N.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extend to any novel one, or any novel combination, of the features

disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

1. A process for preparing a polyamine compound which includes a step (a) of treating a compound which incorporates a moiety of formula:

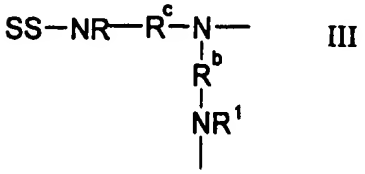
$$SS\text{-}NR\text{-}R^c\text{-}NH\text{-} \qquad I$$

with a compound which incorporates a moiety of formula:

$$-NR^1\text{-}R^b\text{-}L \qquad II$$

and optionally derivatising the product of the reaction, wherein SS represents a solid support and linking means for linking the group -NR- of moiety I to the support, R represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^1 represents a hydrogen atom or an optionally-substituted alkyl or aryl group, R^b and R^c each independently represents an optionally-substituted alkylene or alkenylene group and L represents a leaving group.

2. A process according to claim 1, wherein said process produces a compound which incorporates a moiety:



III

3. A process according to claim 1 or claim 2, wherein said moiety of formula I is part of a structure of formula:

$SS-NR-R^c-NHP^1$ IV

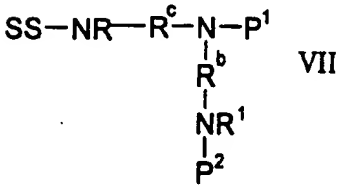
wherein P^1 represents a protecting and/or activating group.

4. A process according to any preceding claim, wherein said moiety of formula II is part of a structure of formula:

$P^2NR^1-R^b-L$

wherein P^2 represents a protecting group.

5. A process according to any preceding claim, wherein the product of the reaction of moieties of formula I and II is of formula



VII

wherein P^1 represents a protecting and/or activating group and P^2 represents a protecting group.

6. A process according to any preceding claim, wherein the polyamine prepared by reacting moieties I and II and/or moiety III and/or moiety VII are derivatised in a subsequent process step.

7. A process according to claim 6, wherein derivatisation involves treatment with a first reagent in order to incorporate a residue of said first reagent into said polyamine.

8. A process according to claim 7, wherein said first reagent is difunctional.

9. A process according to claim 7 or claim 8, wherein said first reagent includes an amine group or a precursor of an amine group.

10. A process according to any of claims 7 to 9, wherein said first reagent is an amino acid or a precursor thereof.

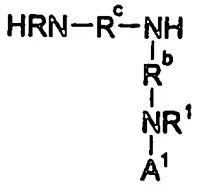
11. A process according to any of claims 7 to 10, wherein said polyamine is derivatised with a second reagent.

12. A process according to any preceding claim, wherein R represents a hydrogen atom or an optionally-substituted alkyl group; R^b and R^c independently have up to 10 carbon atoms in a straight chain; R^1 represents a hydrogen atom or an optionally-substituted C_{1-10} alkyl group or an optionally-substituted aryl group.

13. A process according to any preceding claim, wherein L is an electron-withdrawing group.

14. A process according to any preceding claim, wherein L represents a halogen atom or an hydroxy group.

15. A process according to any preceding claim, wherein the compound prepared in the process is of general formula



wherein A^1 is a substituent group.

16. A process for preparing a plurality of different polyamine compounds which includes a step of:

(a) selecting a plurality of different compounds which include moiety I and/or a plurality of different compounds which include moiety II and reacting compound(s) of formula I with compound(s) of formula II, followed by optional derivatisation thereby to prepare a plurality of different polyamine compounds; OR

(b) derivatising a product of a reaction of a moiety I with a moiety II with a plurality of different compounds, followed by optional derivatisation of the product thereof, thereby to prepare a plurality of different polyamine compounds;

wherein moieties I and II are as described in any preceding claim.

17. A library of compounds prepared in a process according to claim 16.

18. A product of a process described in any of claims 1 to 16.

19. Any novel intermediate of a process described in any of claims 1 to 16.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
APB/MER/Q269		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 01719	16/06/1999	16/12/1998
Applicant		
CAMBRIDGE COMBINATORIAL LIMITED et. al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed. unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   COMBINATORIAL PROCESS FOR PREPARING POLYAMINES

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
GB 99/01719

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 18-19
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The claims nos. 18 and 19 are distinguished by no feature, both stuctural and functional, making a search impossible.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 18-19

The claims nos. 18 and 19 are distinguished by no feature, both structural and functional, making a search impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]B 99/01719

A. CLASSIFICATION OF SUBJECT MATTE[redacted]
IPC 7 C07K1/04 C07B61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G BYK ETAL.: "Synthesis, activity and structure-activity relationship studies of novel cationic lipids for DNA transfer" JOURNAL OF MEDICINAL CHEMISTRY., vol. 41, no. 2, 15 January 1998 (1998-01-15), pages 224-235, XP002118261 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document --- -/--	1-17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1999	25/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Masturzo, P

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]B 99/01719

C.(Continuation) DOCUMENTS CONSIDERE[redacted]O BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	H AN ET AL.: "Solution phase combinatorial chemistry. Synthesis of novel linear pyridinopolyamine libraries with potent antibacterial activity " JOURNAL OF ORGANIC CHEMISTRY., vol. 62, no. 15, 25 July 1997 (1997-07-25), pages 5156-5164, XP002118262 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 the whole document	1-17
X	CHEMICAL ABSTRACTS, vol. 129, no. 6, 10 August 1998 (1998-08-10) Columbus, Ohio, US; abstract no. 66145, I MARSH ET AL.: "Solid phase polyamine linkers-synthesis and combinatorial utility" XP002118263 & INNOVATION AND PERSPECTIVES IN SOLID PHASE SYNTHESIS. COLLECT. PAP. INTERNATIONAL SYMPOSIUM, 4TH, MEETING DATE 1995 ,1996, pages 111-114, Mayflower Scientific, Birmingham, UK abstract	1-17
X	CHEMICAL ABSTRACTS, vol. 129, no. 21, 23 November 1998 (1998-11-23) Columbus, Ohio, US; abstract no. 275773, G BYK ET AL.: "Novel non-viral vectors for gene delivery: synthesis of a second-generation library of mono-functionalized poly-(guanidinium) amines and their introduction into cationic lipids" XP002118264 & BIOTECHNOLOGY AND BIOENGINEERING., vol. 61, no. 2, 1998, pages 81-87, INTERSCIENCE PUBLISHERS, LONDON., GB ISSN: 0006-3592 abstract	1-17
P,X	WO 99 03823 A (ORIDIGM CORPORATION) 28 January 1999 (1999-01-28) the whole document	1-17

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P[redacted]B 99/01719

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9903823 A	28-01-1999	AU 8496898 A	10-02-1999

PATENT COOPERATION TREATY

3

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
APB/MER/Q269		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01719	16/06/1999	16/12/1998
International Patent Classification (IPC) or national classification and IPC C07K1/04		
Applicant CAMBRIDGE COMBINATORIAL LIMITED et. al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11/07/2000	07.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Döpfer, K-P Telephone No. +49 89 2399 8547

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01719

I. Basis f the r port

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-32 as originally filed

Claims, No.:

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 18, 19.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 18, 19.

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

R It m I

Basis of the report

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No International Search Report has been established for present claims 18 and 19 due to the lack of any distinguishing feature, both structural and functional, which would have made a search possible.
   According to Rule 66.1(e) PCT no International preliminary examination is to be carried out upon these claims.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: G BYK ETAL.: 'Synthesis, activity and structure-activity relationship studies of novel cationic lipids for DNA transfer' JOURNAL OF MEDICINAL CHEMISTRY., vol. 41, no. 2, 15 January 1998 (1998-01-15), pages 224-235, XP002118261 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623

   D2: CHEMICAL ABSTRACTS, vol. 129, no. 6, 10 August 1998 (1998-08-10) Columbus, Ohio, US; abstract no. 66145, I MARSH ET AL.: 'Solid phase polyamine linkers-synthesis and combinatorial utility' XP002118263 & INNOVATION AND PERSPECTIVES IN SOLID PHASE SYNTHESIS. COLLECT. PAP. INTERNATIONAL SYMPOSIUM, 4TH, MEETING DATE 1995 ,1996, pages 111-114, Mayflower Scientific, Birmingham, UK

   D3: CHEMICAL ABSTRACTS, vol. 129, no. 21, 23 November 1998 (1998-11-23) Columbus, Ohio, US; abstract no. 275773, G BYK ET AL.: 'Novel non-viral

vectors for gene delivery: synthesis of a second-generation library of mono-functionalised poly-(guanidinium) amines and their introduction into cationic lipids' XP002118264 & BIOTECHNOLOGY AND BIOENGINEERING., vol. 61, no. 2, 1998, pages 81-87, INTERSCIENCE PUBLISHERS, LONDON., GB ISSN: 0006-3592

D4: WO 99 03823 A (ORIDIGM CORPORATION) 28 January 1999 (1999-01-28)

D5: H AN ET AL.: 'Solution phase combinatorial chemistry. Synthesis of novel linear pyridinopolyamine libraries with potent antibacterial activity ' JOURNAL OF ORGANIC CHEMISTRY., vol. 62, no. 15, 25 July 1997 (1997-07-25), pages 5156-5164, XP002118262 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263

2. The present application relates to a process for preparing a polyamine compound including the reaction of compounds of the type SS-NR-R^c-NH- with compounds incorporating the moiety -NR^1-R^b-L (L: leaving group, R^b, R^c: independently alkylene or alkenylene groups).

The claims address the preparation of polyamines inter alia via solid phase synthesis including combinatorial libraries of such compounds. The prior art documents D1-D3 and D5 disclose subject-matter concerning the synthesis and derivatisation of polyamines which affect the novelty of present claims 1-19 (Article 33(2) PCT).

Furthermore, known compounds which are prepared by an alternative (novel) process do not become novel by this method of preparation (claim 18).

Nevertheless, the examples of the present application disclose polyamines fixed upon an oligopeptide skeleton. This subject-matter appears to be novel over the prior art but it is not claimed as such.

The subject-matter of present claims 1-17 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-99/03823	28.01.1999	15.07.1998	15.07.1997 14.11.1997 15.05.1998

Re Item VII
Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3, D5 is not mentioned in the description, nor are these documents identified therein.

2. The use of the expression "...*incorporated by reference*..." (page 31, line 11 of the description) is not allowed in some designated Contracting States. When entering the Regional/National phase these expressions should be deleted from the application.